1623

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/527,558
Applicant	:	PFIRRMANN
Filed	:	March 16, 2000
TC/A.U.	:	1623
Examiner	:	L. Maier
Docket No.	**:**	**1194-153**
Customer No.	**:**	**6449**

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

Dear Sir:

Enclosed in connection with the above-referenced application is an Appeal Brief with Appendix in triplicate.

Also, please charge the $160.00 fee to our Deposit Account No. 02-2135. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

By _____

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE		
	Application Number	09/527,558
	Filing Date	March 16, 2000
	First Named Inventor	PFIRRMANN
	Group Art Unit	1623
	Examiner Name	L. MAIER
	Attorney Docket Number	1194-153
Title of the Invention: *ANTICOAGULANT/STERILIZING COMPOSITIONS AND METHODS*		

APPEAL BRIEF

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This is an appeal from the Office Action dated February 25, 2003 in which the Examiner issued a final rejection of claims 1-4, 13, and 24-34 under 35 U.S.C. 103(a). A Notice of Appeal was filed on July 25, 2003.

Real Party in Interest

The owner of the above-referenced patent application and the real party in interest in this appeal is the assignee, Ed. Geistlich Söehne AG für chemische Industrie, of Switzerland.

Related Appeals and Interferences

Applicant is unaware of any other appeals or interferences related to the subject matter of this appeal.

Status of Claims

Claims 1-4, 13, and 24-34 are pending and were finally rejected as a result of the Office

Action dated February 25, 2003. Applicant appeals from the rejection of claims 1-4, 13, and 24-34. The appealed claims are reproduced in the appendix attached hereto. Claims 5-12 and 14-20 have been canceled and claims 21-23 have been withdrawn from consideration.

Status of Amendments

There have been no amendments filed subsequent to the last rejection of the claims as presently pending.

Summary of The Invention

In accordance with the present invention, a composition and method is provided for preventing thrombosis formation on a liquid-contacting surface of a liquid delivery system that is connected to a patient for delivery of a liquid to the patient. The invention comprises a method of preventing thrombosis which utilizes one of two alternative regimens, both of which include the administration of two or more anticoagulants to the patient. The first regimen involves forming a seal in the liquid delivery system with a thrombosis-preventing liquid containing taurolidine, taurultam or a mixture thereof and an additional anticoagulant agent. In an alternative regimen, the liquid-contacting surface of the delivery system is contacted with a solution containing an anticoagulant agent, and thereafter contacted with a solution containing taurolidine, taurultam or a mixture thereof, with the two contacting steps repeated between administration of liquids to the patient.

Claim 1 recites a method of preventing thrombosis formation on a liquid-containing surface of a liquid delivery system, the liquid delivery system being connected to a patient for delivery of a liquid to said patient, the method comprising forming a seal in the liquid delivery

system between delivery of liquids using a thrombosis-preventing liquid containing taurolidine, taurultam or a mixture thereof, said thrombosis-preventing liquid further containing an anticoagulant agent other than taurolidine or taurultam.

Claim 24 recites a method of preventing thrombosis formation on a liquid-containing surface of a liquid delivery system, the liquid delivery system being connected to a patient for delivery of a liquid to said patient, the method comprising first contacting said surface with a solution containing a thrombosis-preventing amount of an anticoagulant agent other than taurolidine or taurultam, thereafter contacting said surface with a solution containing taurolidine, taurultam or a mixture thereof, and repeating both of the surface contacting steps between delivery of liquids to said patient.

Applicant has discovered that by forming a seal with a thrombosis-preventing liquid, as set out in the first regimen (claim1), effective anti-thrombotic action can be achieved with unexpectedly small quantities of the liquid. Furthermore, with respect to the second regimen (claim 24), it has been found that the first and second solutions can be sequentially applied avoiding possible complications or interactions resulting from mixing the added anticoagulant agent and taurolidine/taurultam. The two step application process is then repeated between delivery of liquid to a patient.

The invention thus comprises a method of either forming a seal with a solution in the liquid delivery system or alternatively contacting the liquid containing surface with two different solutions in a sequential and repetitive manner, both procedures employed to prevent thrombosis formation on the surface of the liquid delivery system.

Issues

The following issues are presented by this appeal:

1) Whether claims 1-4 and 13 were properly rejected under 35 U.S.C. 103(a) as unpatentable over Lehner (WO 98/28027; "Lehner") in view of Reinmuller (U.S. Patent NO. 5,077,281; "Reinmuller"); and

2) Whether claims 24-34 were properly rejected under 35 U.S.C. 103(a) as unpatentable over Lehner (WO 98/28027; "Lehner") in view of Raad et al. (U.S. Patent NO. 5,688,516; "Raad"); and

3)Whether claims 24-34 were properly rejected under 35 U.S.C. 103(a) as unpatentable over Lehner (WO 98/28027; "Lehner") and Raad et al. (U.S. Patent NO. 5,688,516; "Raad") in further view of Ito et al. (U.S. Patent NO. 5,167,960; "Ito").

Grouping of Claims

For purposes of the rejection under 35 U.S.C. § 103(a), Issue 1 set forth above, claims 1 and 13 stand together, and claims 2-4 each stand alone.

For purposes of the rejection under 35 U.S.C. § 103(a), Issue 2 set forth above, claims 24 and 32 stand together, claims 25 and 29 stand together, claims 26 and 30 stand together, claims 27 and 31 stand together, claims 33 and 34 stand together, and claim 28 stands alone.

For purposes of the rejection under 35 U.S.C. § 103(a), Issue 3 set forth above, claims 24 and 32-34 stand together, claims 25 and 29 stand together, claims 26 and 30 stand together, and claims 27 and 31 stand together, and claim 28 stands alone.

Argument

1. Claims 1-4 and 13 are nonobvious over Lehner and Reinmuller.

Claims 1-4 and 13 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lehner in view of Reinmuller.

In order for references to render a claim obvious, the references must at least suggest the features of the claim and their combination to a person having ordinary skill in the art. In the present case, the combination of references does not teach or suggest the use of taurolidine or taurultam or a mixture thereof in combination with another anti-coagulant agent to prevent thrombosis formation on a liquid-containing surface of a liquid delivery system by forming a seal in the liquid delivery system.

Lehner discloses flushing or sealing a liquid delivery system with taurolidine or taurultam for the purpose of combating infection or sepsis. Reinmuller discloses a method for the prevention of thrombosis, teaching the use of taurolidine or taurultam as an anticoagulant contacted with a surface and further suggesting that these compounds may be used **together** with known anti-coagulants such as heparin.

Lehner does not teach or suggest preventing thrombosis formation. Reinmuller does not teach or suggest a method which would encompass flushing or sealing a liquid in or on the surface of a liquid delivery system. In contrast to these two references, the present claims 1-4 and 13 are to a method whereby thrombosis is prevented by sealing a delivery system with a solution containing taurolidine or taurultam combined with an additional anti-coagulant to prevent thrombosis formation.

Applicable case law holds that in order to render a claim obvious, the prior art must teach

or suggest all of the features of the claim and their combination to a person having ordinary skill in the art. The test for obviousness under 35 U.S.C. ¶103 (a) is set forth by the United States Supreme Court in *Graham v. John Deere, Co.*, 383 U.S. 1, 17-18 (1966). As mandated therein, in an obviousness determination under ¶103, the scope and content of the prior art are to be determined, the differences between the prior art and the claims at issue are to be ascertained and the level of ordinary skill in the pertinent art resolved.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

Since the combination of references cited by the Examiner does not teach or suggest any modification whatsoever of the prior art to arrive at the present invention, a finding of obviousness could only arise through some motivation to combine the references. When the motivation to combine the teachings of the references is not immediately apparent, it is the duty of the examiner to explain why the combination of the teachings is proper. *Ex parte Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Inter. 1986). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior

art, not in applicant's disclosure. *In re Vaeck,* 947 F.2d at 493.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984). A suggestion, teaching or motivation to combine the prior art references is an "essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. MP3 Sys., Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998). Furthermore, the suggestion must be clear and particular; "broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence'". *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000). In reversing a finding of obviousness by the Board of Patent Appeals and Interferences, the Federal Circuit recently noted that "[t]he need for specificity **pervades** this authority." *In re Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q. 2d 1430, 1433 (Fed. Cir. 2002) (*emphasis added; citing In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000): "particular findings must be made as to the reason the skilled artisan , with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.") In particular, evidence of obviousness must provide an " impetus . . . to cause one skilled in the art to combine the teachings of the references to make the proposed modification." *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1301, n.2 (*citing In re Albrecht*, 185 U.S.P.Q. 585 (C.C.P.A. 1975)). The combination of cited art must provide evidence of the motivating force which would motivate one to do what the applicant has done.

The issue is not whether the combination could have been done, but whether the contents

of the prior art references provide motivation to make the combination. Accordingly, in the present case, the Examiner cannot establish obviousness by locating references which describe various aspects of Appellants' invention without also providing evidence that one skilled in the art would have been motivated to combine the separate components. Based on the pervasive authority in this area, it is well-established that the Examiner cannot merely assert the possibility of the combination.

In the present case, there is no motivation in the prior art for the proposed combination. First, Lehner does not serve the same purpose or function as the present invention. Lehner is concerned with the prevention of infection or sepsis, while Reinmuller and the present invention are directed to the prevention of thrombosis. There would be no motivation or suggestion for one seeking to prevent sepsis to look to the anti-thrombolytic teachings of Reinmuller. There would similarly be no motivation or suggestion for one seeking to prevent thrombosis to look to the anti-microbial teachings of Lehner.

Assuming, *arguendo* that the skilled artisan examined Reinmuller in an effort to improve the teachings of Lehner, while Applicant believes that there is no inherent anti-coagulant activities of taurolidine or taurultam, there is nothing in Reinmuller to suggest adding an additional anticoagulant to prevent sepsis. In analogous manner, if the skilled artisan examined Lehner in an effort to improve Reinmuller, nothing in Lehner would suggest application of an antimicrobial seal in order to prevent thrombosis.

The Examiner states at page 3 of Paper No. 22 that "Lehner teaches that taurolidine can reduce the adhesiveness of fibrin deposits which lead to thrombosis. Furthermore, Reinmuller

also recognizes the dual funtionality (bacteriocidal and coagulation-inhibiting action) of the taurolin derivatives in the reference. The Examiner maintains that one of ordinary skill, having the teaching of Lehner and Reinmuller, would recognize that sealing a taurolin derivative alone in the liquid-delivery system would be reasonably expected to prevent thrombosis. The addition of another anticoagulant would be obvious for the additive effect."

First of all, there are no inherent anti-coagulant activities of taurolidine or taurultam. Reinmuller was mistakenly lead to this belief because the blood he used was blood for transfusion and already contained heparin.

Thus, the assertion in Paper No. 22 that the addition of another anticoagulant would be obvious for the additive affect, is the Examiner's suggestion, and is without any basis in fact.

No combination of the prior art would result in the present invention as specified in claim 1, since none of the prior art suggest sealing a delivery system with a solution containing taurolidine or taurultam **combined with** an additional anticoagulant, whether to prevent sepsis or thrombosis.

As the Federal Circuit has noted in *In re Rouffet*, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998) "...an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *Id.* at 1457. The court in Rouffet went on to state, "[t]o prevent the use of

hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness."*Id.* at 1457-58.

Claim 1 is the only independent claim rejected under 35 U.S.C. §103(a) as being unpatentable over Lehner in view of Reinmuller. Claim 13 recites a method as in claim 1 wherein the solution or liquid containing taurolidine, taurultam or a mixture thereof contains from about 0.5 to about 3% by weight of taurolidine, or from about 1 to about 7.5% by weight of taurultam. These claims stand rejected without any well reasoned or valid explanation as to what would provide motivation to a person having ordinary skill in the art to combine the teachings of Lehner and Reinmuller to arrive at the presently claimed invention as claimed in claim 1 and dependent claim 13. It is submitted that the Examiner's assertion of obviousness based on these references is improper because it is supported by no more than the application of hindsight to the prior art, in light of the Applicant's own disclosure.

Claim 2 depends from claim 1 and further recites a method for preventing thrombosis wherein the thrombosis preventing solution is contacted with the surface of the liquid delivery system for at least about 1 hour. Claim 2 is nonobvious over a combination of Lehner and Reinmuller for all of the reasons applied to claim 1 above. Furthermore, claim 2 is nonobvious over a combination of Lehner and Reinmuller for the separate and distinct reason that a combination of these references does not teach or suggest a method as in claim 1 wherein the thrombosis preventing solution is contacted with the surface of the liquid delivery system for at least about 1 hour.

Claim 3 depends from claim 2 and further recites a method for preventing thrombosis wherein said solution or liquid containing taurolidine, taurultam or mixture thereof is sealed in said delivery system for a period of at least 12 hours. Claim 3 is nonobvious over a combination of Lehner and Reinmuller for all of the reasons applied to claim 2 above. Furthermore, claim 3 is nonobvious over Lehner and Reinmuller for the separate and distinct reason that a combination of these references do not teach or suggest a method for preventing thrombosis as in claim 2 wherein said solution containing taurolidine, taurultam or mixture thereof is sealed in said delivery system for a period of at least 12 hours.

Claim 4 depends from claim 3 and recites a method for preventing thrombosis wherein said taurolidine, taurultam or a mixture thereof which is sealed in said delivery system is replaced at least about daily. Claim 4 is nonobvious over a combination of Lehner and Reinmuller for all of the reasons applied to claim 3 above. Furthermore, claim 4 is nonobvious over a combination of Lehner and Reinmuller for the separate and distinct reason that a combination of these references does not teach or suggest a method for preventing thrombosis wherein said taurolidine, taurultam or a mixture thereof which is sealed in said delivery system is replaced at least about daily.

Based on the foregoing, the Applicant respectfully submits that claims 1-4 and 13 of the present application are nonobvious over a combination of Lehner and Reinmuller and requests withdrawal of this rejection.

2. Claims 24-34 are nonobvious over Lehner in view of Raad.

Claims 24-34 were rejected under 35 U.S.C. 103(a) as unpatentable over Lehner in view

of Raad.

The above-noted deficiencies of the Lehner reference are equally applicable here, and incorporated herein by reference.

The Raad et al patent discloses flushing of a catheter with heparin, and teaches other known anticoagulants. However, the Raad et al. reference cannot be combined with the Lehner reference to suggest the specifically claimed features of:

- first contacting a surface with an anticoagulant solution other than taurolidine or taurultam,
- thereafter contacting the surface with a solution containing taurolidine, taurultam or a mixture thereof, and
- repeating both of the contacting steps between delivery of liquids to the patient.

Claim 24 discloses a method of preventing thrombosis in a liquid-delivery system by **first contacting** the surface with a solution containing a thrombosis-preventing amount of an anticoagulant agent other than taurolidine or taurultam, **then contacting** the surface with a solution containing taurolidine, taurultam or a mixture thereof and **repeating** the contacting steps between delivery of liquids to the patient. Neither reference suggests repeating such a two-step process between administration of liquids to the patient to prevent thrombosis. Raad is directed towards an isolated instance of flushing or coating a catheter with an solution of anticoagulants and antibiotics. Thus, Raad actually teaches away from the repetitive two-step process as set out in claim 24. After being led away from the present invention by the teachings of Raad, nothing in Lehner would return a person having ordinary skill in the art to the concept of contacting the

surface with two distinct anticoagulant compositions in sequence, repeating the process between delivery of a liquid.

Here, the Examiner has not pointed to any evidence, either in the references or the general knowledge of the prior art, of a suggestion or motivation to combine the references as set forth in the claims. The broad conclusory statement by the Examiner that it would be obvious to combine these two references, either based on what is taught therein, or based on the level of ordinary skill in the art, is completely unsupported.

Claim 28 depends from claim 24 and recites a method wherein the anticoagulant-containing solution is contacted with said surface by injecting the solution into the liquid delivery containing solution and then removing the anti-coagulant containing solution from the delivery system. Claim 28 is nonobvious over a combination of Lehner and Raad for all of all of the reasons applied to claim 24 above. Furthermore, claim 28 is nonobvious over a combination of Lehner and Raad for the separate and distinct reason that a combination of these references does not teach or suggest a method of preventing thrombosis on a liquid-contacting surface wherein the anticoagulant-containing solution is contacted with said surface by injecting the solution into the liquid delivery containing solution and then removing the anti-coagulant containing solution from the delivery system.

Claims 25 and 29 depend from claims 24 and 28 respectively and further recite a method for preventing thrombosis wherein the thrombosis preventing solution is contacted with the surface of the liquid delivery system for at least about 1 hour.

Claims 25 and 29 are nonobvious over a combination of Lehner and Raad for all of the

reasons applied to claim 24 and 28 above. Furthermore, claims 25 and 29 are nonobvious over a combination of Lehner and Raad for the separate and distinct reason that a combination of these references does not teach or suggest a method as in claim 24 and 28, wherein the thrombosis preventing solution is contacted with the surface of the liquid delivery system for at least about 1 hour.

Claims 26 and 30 depend from claims 25 and 29 respectively and further recite a method for preventing thrombosis wherein said solution or liquid containing taurolidine, taurultam or mixture thereof is sealed in said delivery system for a period of at least 12 hours. Claims 26 and 30 are nonobvious over a combination of Lehner and Raad for all of the reasons applied to claims 25 and 29 above. Furthermore, claims 26 and 30 are nonobvious over Lehner and Raad for the separate and distinct reason that a combination of these references do not teach or suggest a method for preventing thrombosis as in claim 25 and 29, wherein said solution containing taurolidine, taurultam or mixture thereof is sealed in said delivery system for a period of at least 12 hours.

Claims 27 and 31 depend from claims 26 and 30 respectively and recite a method for preventing thrombosis wherein said taurolidine, taurultam or a mixture thereof which is sealed in said delivery system is replaced at least about daily. Claims 27 and 31 are nonobvious over a combination of Lehner and Raad for all of the reasons applied to claims 26 and 30 above. Furthermore, claims 27 and 31 are nonobvious over a combination of Lehner and Raad for the separate and distinct reason that a combination of these references does not teach or suggest a method for preventing thrombosis wherein said taurolidine, taurultam or a mixture thereof which

is sealed in said delivery system is replaced at least about daily.

Claims 33 and 34 depend from claim 24 and further recite a method for preventing thrombosis wherein the anticoagulant solution is selected from the group consisting of sodium citrate, aprotinin, hirudin, desirudin, danaparoid, danaparoid-sodium, heparin, pentosan, pentosanpolysulfate-sodium, ticlopidine, clopidogrel, and mixtures thereof or is present in an amount within a range of from about 0.1-10 mg. For the same reasons as applied to claim 24, claims 33 and 34 are nonobvious over a combination of Lehner and Raad. Furthermore, claims 33 and 34 are nonobvious over a combination of Lehner and Raad for the separate and distinct reason that a combination of these references does not teach or suggest a method for preventing thrombosis as in claim 24 wherein the anticoagulant solution is selected from the group consisting of sodium citrate, aprotinin, hirudin, desirudin, danaparoid, danaparoid-sodium, heparin, pentosan, pentosanpolysulfate-sodium, ticlopidine, clopidogrel, and mixtures thereof or is present in an amount within a range of from about 0.1-10 mg.

As noted above, in order for references to render a claim obvious, the references must at least suggest each of the features of the claims and their combination.

In the present case, the combination of Lehner and Raad does not suggest the above-noted features or their combination. Accordingly, claims 24-34 are nonobvious over Lehner in view of Raad.

3. Claims 24-34 are nonobvious over Lehner and Raad in view of Ito.

Claims 24-34 were also rejected under 35 U.S.C. §103(a) as being unpatentable over Lehner and Raad further in view of Ito *et al.*, U.S. 5,167,960 (Ito). The Examiner has cited Ito

for disclosing the use of hirudin or a hirudin derivative that can be utilized to inhibit thrombosis on implantable and extracorporeal devices. The Examiner is of the opinion that Ito teaches anticoagulants including hirudin and its derivatives and further alleges that it would have been obvious to substitute any art-disclosed anticoagulant and further that a person having ordinary skill in the art could readily determine optimum time and concentrations of their administration.

Regardless of the disclosure of Ito as applied by the Examiner, this reference does nothing to remedy the basic deficiencies of Lehner and Raad discussed above. Accordingly, no combination of the cited references would result in the method as set out in claim 24. Thus, for the same reasons as applied to claim 24 in the previous argument, it is respectfully submitted that claim 24 is nonobvious over a combination of Lehner, Raad and Ito.

Claim 28 depends from claim 24 and recites a method wherein the anticoagulant-containing solution is contacted with said surface by injecting the solution into the liquid delivery containing solution and then removing the anti-coagulant containing solution from the delivery system. Claim 28 is nonobvious over a combination of Lehner and Raad in view of Ito for all of all of the reasons applied to claim 24 above. Furthermore, claim 28 is nonobvious over a combination of Lehner and Raad in view of Ito for the separate and distinct reason that a combination of these references does not teach or suggest a method of preventing thrombosis on a liquid-contacting surface wherein the anticoagulant-containing solution is contacted with said surface by injecting the solution into the liquid delivery containing solution and then removing the anti-coagulant containing solution from the delivery system.

Claims 25 and 29 depend from claims 24 and 28 respectively and further recite a method

for preventing thrombosis wherein the thrombosis preventing solution is contacted with the surface of the liquid delivery system for at least about 1 hour.

Claims 25 and 29 are nonobvious over a combination of Lehner and Raad in view of Ito for all of the reasons applied to claim 24 and 28 above. Furthermore, claims 25 and 29 are nonobvious over a combination of Lehner and Raad in view of Ito for the separate and distinct reason that a combination of these references does not teach or suggest a method as in claim 24 and 28, wherein the thrombosis preventing solution is contacted with the surface of the liquid delivery system for at least about 1 hour.

Claims 26 and 30 depend from claims 25 and 29 respectively and further recite a method for preventing thrombosis wherein said solution or liquid containing taurolidine, taurultam or mixture thereof is sealed in said delivery system for a period of at least 12 hours. Claims 26 and 30 are nonobvious over a combination of Lehner and Raad in view of Ito for all of the reasons applied to claims 25 and 29 above. Furthermore, claims 26 and 30 are nonobvious over Lehner and Raad in view of Ito for the separate and distinct reason that a combination of these references do not teach or suggest a method for preventing thrombosis as in claim 25 and 29, wherein said solution containing taurolidine, taurultam or mixture thereof is sealed in said delivery system for a period of at least 12 hours.

Claims 27 and 31 depend from claims 26 and 30 respectively and recite a method for preventing thrombosis wherein said taurolidine, taurultam or a mixture thereof which is sealed in said delivery system is replaced at least about daily. Claims 27 and 31 are nonobvious over a combination of Lehner and Raad in view of Ito for all of the reasons applied to claims 26 and 30

above. Furthermore, claims 27 and 31 are nonobvious over a combination of Lehner and Raad in view of Ito for the separate and distinct reason that a combination of these references does not teach or suggest a method for preventing thrombosis wherein said taurolidine, taurultam or a mixture thereof which is sealed in said delivery system is replaced at least about daily.

As noted above, in order for references to render a claim obvious, the references must at least suggest each of the features of the claims and their combination.

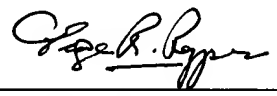
In the present case, the combination of Lehner and Raad in view of Ito does not suggest the above-noted features or their combination.

Based on the foregoing, Applicant submits that claims 24-34 are nonobvious over Lehner and Raad in view of Ito and requests withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that all grounds of rejection of claims 1-4, 13, and 24-34 are unsupportable on the record and thus improper. The Honorable Board is therefore respectfully requested to reverse all grounds of rejection and to direct the passage of this application to issue.

Respectfully submitted,

By: 

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APPENDIX

1. A method of preventing thrombosis formation on a liquid-containing surface of a liquid delivery system, the liquid delivery system being connected to a patient for delivery of a liquid to said patient, the method comprising forming a seal in the liquid delivery system between delivery of liquids using a thrombosis-preventing liquid containing taurolidine, taurultam or a mixture thereof, said thrombosis-preventing liquid further containing an anticoagulant agent other than taurolidine or taurultam.

2. The method of claim 1 wherein the liquid containing taurolidine, taurultam or mixture thereof is contacted with said surface for at least about 1 hour.

3. The method of claim 2 wherein said liquid containing taurolidine, taurultam or mixture thereof is sealed in said delivery system for a period of at least 12 hours.

4. The method of claim 3 wherein said liquid containing taurolidine, taurultam or mixture thereof which is sealed in said delivery system, is replaced at least about daily.

13. The method of claim 1 wherein said liquid containing taurolidine, taurultam or a mixture thereof contains from about 0.5 to about 3% by weight of taurolidine, or from about 1 to about 7.5% by weight of taurultam.

24. A method of preventing thrombosis formation on a liquid-containing surface of a liquid delivery system, the liquid delivery system being connected to a patient for delivery of a liquid to said patient, the method comprising first contacting said surface with a solution containing a thrombosis-preventing amount of an anticoagulant agent other than taurolidine or taurultam, thereafter contacting said surface with a solution containing taurolidine, taurultam or a mixture thereof, and repeating both of the surface contacting steps between delivery of liquids to said

patient.

25. The method of claim 24 wherein the solution containing taurolidine, taurultam or mixture thereof is contacted with said surface for at least about 1 hour.

26. The method of claim 25 wherein said solution containing taurolidine, taurultam or mixture thereof is sealed in said delivery system for a period of at least 12 hours.

27. The method of claim 26 wherein said solution containing taurolidine, taurultam or mixture thereof which is sealed in said delivery system, is replaced at least about daily.

28. The method of claim 24 wherein the anticoagulant-containing solution is contacted with said surface by injecting the anticoagulant-containing solution into said liquid delivery system and then removing said anticoagulant-containing solution from said liquid delivery system.

29. The method of claim 28 wherein the solution containing taurolidine, taurultam or a mixture thereof is contacted with said surface for at least about 1 hour.

30. The method of claim 29 wherein said solution containing taurolidine, taurultam or a mixture thereof is sealed in said delivery system for a period of at least about 12 hours.

31. The method of claim 30 wherein the solution containing taurolidine, taurultam or a mixture thereof which is sealed in said delivery system is replaced at least about daily.

32. The method of claim 24 wherein said solution containing taurolidine, taurultam or a mixture thereof contains from about 0.5 to about 3% by weight of taurolidine, or from about 1 to about 7.5% by weight of taurultam.

33. The method of claim 24 wherein said anticoagulant agent is selected from the group consisting of sodium citrate, aprotinin, hirudin, desirudin, danaparoid, danaparoid-sodium, heparin, pentosan, pentosanpolysulfate-sodium, ticlopidine, clopidogrel, and mixtures thereof.

34. The method of claim 33 wherein said anticoagulant agent is present in an amount within a range of from about 0.1-10mg.